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EXAMINER	
ROBINSON, HOPE A	
ART UNIT	**PAPER NUMBER**
1653	

DATE MAILED: 03/11/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/823,203	LAN ET AL.	
	Examiner	Art Unit	
	Hope A. Robinson	1653	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *20 December 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-11* is/are pending in the application.

4a) Of the above claim(s) *1-7* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *8-11* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *13 April 2004* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Application Status

1. Applicant's election with traverse of Group III (claims 8-11) on December 20, 2004 is acknowledged. Claims 1-7 are withdrawn from further consideration pursuant to 37 CFR 1.12(b), as being drawn to a non-elected invention, there being no allowable generic or linking claim.

Restriction Requirement

2. The traversal is on the grounds that Groups I-III should be rejoined because there is no serious burden of search. Applicant states that although the inventions are independent and distinct the Groups should be rejoined. It is further stated that as the nucleic acid encodes the protein Groups I and II should be rejoined. This argument is not persuasive. The DNA and protein are independent and distinct, having different structures, function and modes of operation. Although the DNA encodes the protein, the DNA can be used to make probes or primers or used in a hybridization assay. Further, the protein can be used to make antibodies or in a bioassay. Regarding search burden, the inventions have acquired a separate status in the art based on the Classification and a reference that would anticipate or make obvious one Group would not necessarily render obvious or anticipate the other Groups. For example, Atshaves et al. (Journal of Lipid Research, vol. 44, pages 1751-1762, 2003) disclose sterol carrier protein-2, however, does not disclose a method to identify an agonist or antagonist of

said protein. The search of each invention is not coextensive. Thus, burden of search is established. Moreover, MPEP chapter 800 indicates that a restriction requirement is proper if the invention is independent and or distinct. Therefore the restriction requirement is deemed proper and is final.

Specification

3. The specification is objected to because of the following informalities:

(a) The specification is objected to because trademarks are disclosed throughout the instant specification and not all of them are capitalized or accompanied by the generic terminology. The use of the trademarks such as TRITON®, TRIS®, for example, have been noted in this application (see page 40). It should be capitalized wherever it appears and be accompanied by the generic terminology. Although the use of trademarks is permissible in patent applications, the proprietary nature of the marks should be respected and every effort made to prevent their use in any manner, which might adversely affect their validity as trademarks. It is suggested that the specification is amended to delete "Tris-HCl" for example, and insert " TRIS® HCL (hydroxymethyl) aminomethane hydrochloride".

(b) The specification is also objected to because it contains an embedded hyperlink and/or other form of browser-executable code. Applicant is required to delete the embedded hyperlink and/or other form of browser-executable code. See MPEP § 608.01. See pages 44 and 47 for example. It is suggested that http:// is deleted.

Correction of the above is required.

Drawing

4. The drawings are objected to because Figure 2 has several sequences, however, only one sequence identifier is present, SEQ ID NO:3. It appears that the sequences listed do not all correspond to SEQ ID NO:3. Corrected drawing sheets in compliance with 37 CFR 1.121(d) are required in reply to the Office action to avoid abandonment of the application. Any amended replacement drawing sheet should include all of the figures appearing on the immediate prior version of the sheet, even if only one figure is being amended. The figure or figure number of an amended drawing should not be labeled as "amended." If a drawing figure is to be canceled, the appropriate figure must be removed from the replacement sheet, and where necessary, the remaining figures must be renumbered and appropriate changes made to the brief description of the several views of the drawings for consistency. Additional replacement sheets may be necessary to show the renumbering of the remaining figures. Each drawing sheet submitted after the filing date of an application must be labeled in the top margin as either "Replacement Sheet" or "New Sheet" pursuant to 37 CFR 1.121(d). If the changes are not accepted by the examiner, the applicant will be notified and informed of any required corrective action in the next Office action. The objection to the drawings will not be held in abeyance. Applicant is reminded to file Formal Drawings.

Sequence Compliance

5. This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 CFR1.821 through 1.825; applicant's attention is directed to the final rule making notice published at 55 FR 18230 (May 1, 1990), and 1114 OG 29 (May 15, 1990). To be in compliance, applicant is required to identify all amino acid sequences of at least 4 L-amino acids and at least 10 nucleotides by a sequence identifier, i.e., "SEQ ID NO:". The specification discloses sequences that have not been identified by a sequence identifier, see for example, page 38, lines 12-13. If these sequences have not been disclosed in the computer readable form of the sequence listing and the paper copy thereof, applicant must provide a computer readable form of the "Sequence Listing" including these sequences, a paper copy of the "Sequence Listing", as well as an amendment directing its entry into the specification, and a statement that the content of the paper and computer readable form copies are the same and, where applicable, include no new matter as required by 37 CFR 1.821(e) or 1.821(f) or 1.821(g) or 1.821(b) or 1.825(d). See the attached Notice to Comply with the sequence rules.

Information Disclosure Statement

6. The Information Disclosure Statement filed on September 10, 2004 has been received and entered. The references cited on the PTO-1449 Form have been considered by the examiner and a copy is attached to the instant Office action.

Claim Objection

7. Claim 9 is objected to because of the following informalities:

Claim 9 is objected to for the recitation of "A method according to claim 8" instead of "The method according to claim 8" (see claim 11 for example).

Correction of the above is required.

Claim Rejections - 35 USC ∋ 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

8. Claims 8-11 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claimed invention is directed to a method for identifying whether a compound is an agonist or antagonist of AeSCP-2 biological activity, however, the specification lacks adequate written description to demonstrate to a skilled artisan that applicant was in possession of the claimed invention. The claimed "biologically active fragment

thereof" is not defined by a structure or function. In addition, based on the open language "comprising", the claimed fragment is unlimited, thus having an undefined structure. The claims read on several fragments, which have not been adequately described. Therefore, the skilled artisan cannot envision the detailed chemical structure of the claimed protein fragments, thus, claims reciting said protein fragments polypeptide lacks adequate written description.

The instant specification disclose that an AeSCP-2 protein is capable of intracellular cholesterol transport in mosquitoes. The specification lacks adequate written description for the claimed fragments thereof, with regard to size, structure and function (i.e. is function retained or is the fragment non-functional or possess a different function). The specification fails to provide any additional representative species of the claimed genus to show that applicant was in possession of the claimed genus. A representative number of species means that the species, which are adequately described, are representative of the entire genus. The written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice, disclosure of drawings, or by disclosure of relevant identifying characteristics, for example, structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus.

Accordingly, in the absence of sufficient recitation of distinguishing identifying characteristics, the specification does not provide adequate written description of the claimed genus. The claimed genus of protein fragments could include non-functional proteins or proteins with a different function than the one described. Therefore, the genus of claimed fragments encompasses widely variant species. As such, neither the description of the structure and function of SEQ ID NO: 3, for example, capable of intracellular cholesterol transport is sufficient to be representative of the attributes and features of the entire genus. Based on the unlimited variations contemplated one skilled in the art would at best expect a protein that is different or at worst a protein that is not functional.

Vas-Cath Inc. v. Mahurkar, 935 F.2d 1555, 1563-64, 19 USPQ2d 1111, 1117 (Fed. Cir.1991), states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in *possession of the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed*" (See page 1117). The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed" (See *Vas-Cath* at page 1116). The skilled artisan cannot envision the detailed chemical structure of the encompassed genus of polypeptides, and therefore, conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it. The

compound itself is required. *See Fiers v. Revel, 25 USPQ2d 1601 at 1606 (CAFC 1993).*

Therefore, for all these reasons the specification lacks adequate written description, and one of skill in the art cannot reasonably conclude that the applicant had possession of the claimed invention at the time the instant application was filed.

9. Claims 8-11 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the protein set forth in SEQ ID NO: 3, does not reasonably provide enablement for any protein fragment thereof. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims. The enablement requirement refers to the requirement that the specification describe how to make and how to use the invention. There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is undue. These factors include, but are not limited to: Quantity of Experimentation Necessary; Amount of direction or guidance presented; Presence or absence of working examples; Nature of the Invention; State of the prior art and Relative skill of those in the art; Predictability or unpredictability of the art and Breadth of the claims (see *In re Wands, 858 F.2d at 737, 8 USPQ2d at1404 (Fed. Cir. 1988*). The factors most relevant to the instant invention are discussed below.

The amount of experimentation required to practice the claimed invention is undue as the claims encompass an unspecified amount of protein fragments for which there is no indication in the claims or the instant specification that the desired function is retained. Based on the large amount of variability contemplated said protein fragment may not have the function ascribed to SEQ ID NO:3 (AeSCP-2 biological activity), however, the claims are directed to identifying whether a compound is an agonist or antagonist of the AeSCP-2 biological activity. Thus the compound could bind to a protein fragment that may not have AeSCP-2 activity, however, there are no method steps to distinguish these types of fragments. The specification does not describe properties of the claimed fragment, such as size or activity; or demonstrate any such fragment retaining the activity of the native protein.

The instant specification does not demonstrate or provide guidance as to what the structure of the protein will be once modified or if said protein will be functional or exhibit the same properties or characteristics as the native protein. Additionally, there is no data provided demonstrative of a particular portion of the structure that must be conserved. Note that the claims do not have a functional limitation. The art recognizes that the sterol carrier protein-2 family (CSP-2) has the following activities: 1) mediate cholesterol trafficking and metabolism, 2) bind cholesterol with high affinity, 3) intracellular transportation of cholesterol, 4) bind fatty acid and fatty acyl coA, 5)important component of steroid biosynthesis, 6) accelerate conversion of cholesterol to steroids in mitochondria and 7) enhance sterol cycling between microsome and plasma membrane (see Murphy et al., Journal of Lipid Research, vol. 41, pages 788-

796, 2000). The homology of AeSCP-2 to SCP-2 is disclosed as 69% and there is no clear indication that AeSCP-2 has parallel function as SCP-2 (see Krebs et al. Insect Molecular Biology, vol. 12, no. 1, pages 51-60, 2003), therefore, the instant claims and specification needs to provide sufficient information regarding the activity to be altered in the claims. Thus, due to the large quantity of experimentation necessary to generate the infinite number of variants/fragments recited in the claims and possibly screen same for activity and the lack of guidance/direction provided in the instant specification, this is merely an invitation to the skilled artisan to use the current invention as a starting point for further experimentation. Thus, undue experimentation would be required for a skilled artisan to make and/or use the claimed invention commensurate in scope with the claims.

Predictability of which potential changes can be tolerated in a protein's amino acid sequence and obtain the desired activity requires a knowledge of and guidance with regard to which amino acids in the protein's sequence, if any, are tolerant of modification and which are conserved (for example, expectedly intolerant to modification), and detailed knowledge of the ways in which the protein's structure relates to its function. In addition, one skilled in the art would expect any tolerance to modification for a given protein to diminish with each further and additional modification, for example, multiple substitutions. In this case, the necessary guidance has not been provided in the specification. Therefore, while it is known in the art that many amino acid substitutions are possible in any given protein, the positions within the protein's sequence where such amino acid substitutions can be made with a reasonable

expectation of success are limited, as certain positions in the sequence are critical to the protein's structure/function relationship. It is also known in the art that a single nucleotide or amino acid change or mutation can destroy the function of the biomolecule in many cases. For example, various sites or regions directly involved in binding activity and in providing the correct three-dimensional spatial orientation of binding and active sites can be affected (see Wells, Biochemistry, vol. 29, pages 8509-8517, 1990). The instant specification provides no guidance/direction as to which regions of the protein would be tolerant of modifications and which would not, and it provides no working examples of any variant sequence that is encompassed by the claims. It is in no way predictable that randomly selected mutations, such as deletions, substitutions, additions, etc., in the disclosed sequences would result in a protein having activity comparable to the one disclosed. As plural substitutions for example are introduced, their interactions with each other and their effects on the structure and function of the protein is unpredictable. The skilled artisan would recognize the high degree of unpredictability that all the fragments/variants encompassed in the claims would retain the recited function.

The state of the prior art provides evidence for the high degree of unpredictability as stated above. Seffernick et al. (J. Bacteriology, vol. 183, pages 2405-2410, 2001) disclose two polypeptides having 98% sequence identity and 99% sequence identity, differing at only 9 out of 475 amino acids (page 2407, right column, middle and page 2408, Fig. 3). The polypeptides of Seffernick et al. are identical along relatively long stretches of their respective sequences (page 2408, Fig. 3), however, these

polypeptides exhibit distinct functions. The modifications exemplified in the Seffernick et al. reference is small compared to those contemplated and encompassed by the claimed invention (see page 21 of the specification and claim 3, for example). Further, Krebs et al. (Insect Molecular Biology, vol. 12, no. 1, pages 51-60, 2003) disclose that the AeSCP-2 protein is 69% homologous to SCP-2, however, states that it is unclear whether the AeSCP-2 has parallel function as SCP-2 family members (page 52) which demonstrates the unpredictability of the "fragment thereof".

The specification lacks adequate guidance/direction to enable a skilled artisan to practice the claimed invention commensurate in scope with the claims. Furthermore, while recombinant and mutagenesis techniques are known in the art, it is not routine in the art to screen large numbers of mutated proteins where the expectation of obtaining similar activity is unpredictable based on the instant disclosure. The amino acid sequence of a protein determines its structural and functional properties, and predictability of what mutations can be tolerated in a protein's sequence and result in certain activity, which is very complex, and well outside the realm of routine experimentation, because accurate predictions of a protein's function from mere sequence data are limited, therefore, the general knowledge and skill in the art is not sufficient, thus the specification needs to provide an enabling disclosure.

The working examples provided do not rectify the missing information in the instant specification pertaining to the claimed variant. The nature and properties of this claim is difficult to ascertain from the examples provided as one of skill in the art would

have to engage in undue experimentation to construct the variants/fragments of the claimed invention and examine the same for function.

The specification does not provide support for the broad scope of the claims, which encompass an unspecified amount of fragments. The claims broadly read on any fragment thereof for the given sequence (SEQ ID NO: 3). The issue in this case is the breath of the claims in light of the predictability of the art as determined by the number of working examples, the skill level artisan and the guidance presented in the instant specification and the prior art of record. This make and test position is inconsistent with the decisions of *In re Fisher, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970)* where it is stated that "...scope of claims must bear a reasonable correlation to scope of enablement provided by the specification to persons of ordinary skill in the art...". Without sufficient guidance, determination of having the desired biological characteristics is unpredictable and the experimentation left to those skilled in the art is unnecessarily and improperly extensive and undue. See *In re Wands, 858 F.2d at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988)*. Therefore, absent direction/guidance regarding whether the structure of the AeSCP-2 protein can tolerate the modifications contemplated a non-functional protein may result and one of skill in the art would not be able to practice the claimed invention commensurate in scope with the claims.

Thus, for all these reasons, the specification is not considered to be enabling for one skilled in the art to make and use the claimed invention as the amount of experimentation required is undue, due to the broad scope of the claims, the lack of guidance and working examples provided in the specification and the high degree of

unpredictability as evidenced by the state of the prior art, attempting to construct and test variants of the claimed invention would constitute undue experimentation. Making and testing the infinite number of possible fragments to find one that functions as described is undue experimentation. Therefore, applicants have not provided sufficient guidance to enable one of skill in the art to make and use the claimed invention in a manner that reasonably correlates with the scope of the claims, to be considered enabling.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

10. Claims 8-11 are rejected under 35 U.S.C. 112, second paragraph, as failing to set forth the subject matter, which applicant (s) regard as their invention.

Claim 8 (a) and (b) lacks clear antecedent basis for "a biologically active fragment thereof" because the preamble of the claim is directed to AeSCP-2 activity, not the activity of a fragment which absent evidence to the contrary may have a different activity or be non-functional.

Claims 8 and 10 are indefinite for the recitation of "AeSCP-2" because the claim does not recite the corresponding spelled out meaning with the acronym, which could represent a tetrapeptide (i.e. ala-ser-cys-pro). The dependent claims hereto are also included in this rejection because they do not rectify the deficiency.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

11. Claims 8-11 are rejected under 35 U.S.C. 102(a) as being anticipated by Krebs et al. (Insect Molecular Biology, vol. 12, no. 1, pages 51-60, 2003), based on the broad recitation of a biological target, altering AeSCP-2 biological activity, and agonist or antagonist.

Krebs et al. disclose a putative intracellular sterol carrier protein in *Aedes aegypti*, AeSCP-2 (BQ785056) the first found in insects, therefore the structure, SEQ ID NO: 3 recited in the claims is an inherent property (see claims 8 and 11, and page 52, column 1 of the reference).

Krebs et al. disclose a method to determine whether ecdysteriods affect AeSCP-2. AeSCP-2 was determined via a ligand binding assay to have high affinity to cholesterol (claim 9, see page 54, column 1). Krebs et al. report that the protein level of AeSCP-2 increased in 20E-treated gut tissue (page 54, column 2). Further, on page 56, column 2, it is stated that addition of 60 ng/ml 20E in tissue culture increased AeSCP-2 which provides evidence that ecdysteroids can directly regulate cholesterol uptake in

the midgut (see page 56, column 2). Therefore, an agonist of AeSCP-2 (claims 8 and 9).

Krebs et al. determined that ecdysteriods interact with AeSCP-2 such that it increases the amount of protein (page 56, column 2) and performed ligand binding assays, which indicated that AeSCP-2 has a high affinity to cholesterol (page 54, column 1 and page 58, column 1; see claim 10). Therefore, the limitations of the claims are met by this reference.

Conclusion

12. No claims are presently allowable.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Hope A. Robinson whose telephone number is 571-272-0957. The examiner can normally be reached on Monday-Friday.
If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jon P. Weber, can be reached at (571) 272-0925. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Hope Robinson, MS

Patent Examiner 3/4/05